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2018 ABSTRACTS of Poster Presentations

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2018 ABSTRACTS
of Poster Presentations

Dear Colleagues:

Welcome to the annual CNS Summit Abstracts of Poster Presentations supplement to *Innovations in Clinical Neuroscience*. We are pleased to provide you with this reference guide to some of the innovative research that is being presented during CNS Summit 2018. The supplement is also available online by visiting www.innovationscns.com.

This supplement is just a small representation of what has become the premier event each year in drug development. Over 500 leaders in the field are attending this year's CNS Summit to experience more enlightening talks and innovative reveals than ever before. Here at the CNS Summit, participants will discover the latest advances in pharmaceutical research and development, such as digital biomarkers, mobile medicine, and AI and machine learning, as well as witness the unveiling of several new innovative products and technologies. Additionally, through the proprietary CNS Summit One-to-One Meeting Platform, participants have the unique opportunity to network with the key stakeholders involved in the discovery and development of new compounds and therapies in medicine.

The CNS Summit is committed to collaboration among all entities involved in drug development, and we believe collaboration and data sharing with those involved in research across a wide variety of disease states will create more opportunity for developing better, safer, and more accessible drugs universally and within all areas of healthcare.

In this abstract supplement, we've organized CNS Summit 2018 poster abstracts into the following groups for your convenience and easy reference:

- Digital Tools and Technology
- Early Identification, Predictive Tools, and Imaging
- Investigative Drug Compounds and Therapies
- Mobile Technology
- Patient Assessment
- Patient Recruitment
- Placebo Response
- Rater Assessment and Training
- Trial Protocol

You will also find an alphabetical index by author and poster title on pages 18 and 19 of this publication.

We hope you find the CNS Summit 2018 poster abstract supplement informative and that it provides a useful snapshot of the research being presented at CNS Summit 2018. Make sure to mark your calendars for CNS Summit 2019, which will take place October 31 – November 3, 2019, at the Boca Raton Resort in Florida. Visit www.cnssummit.org for more information.

Hope to see you in Boca! As always, we welcome your feedback and participation.

Sincerely,

Amir Kalali, MD
Editor, *Innovations in Clinical Neuroscience* **ICNS**

CNS Summit 2018—Abstracts of Poster Presentations

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CNS Summit:
Selected Abstracts from the 2018 Meeting

DIGITAL TOOLS AND TECHNOLOGY

Agile development of a prescription digital therapeutic for patients with schizophrenia

Presenters: Campellone TR, Smayda KE, and Maricich YA

Affiliations: Pear Therapeutics, Boston, Massachusetts

Objective: With software-based "digital" therapeutic interventions, product development is agile and data-driven, allowing for continuous product refinement. Compared to existing models of therapeutic development, this approach allows for more rapid clinical validation while creating a safer, more efficacious treatment. Here, we illustrate agile product development with Pear 004, a prescription digital therapeutic for patients with schizophrenia delivered in conjunction with standard of care.

Design: We employed data collected from user research (clinicians and patients) and two translational studies conducted in patients with schizophrenia. In these studies, we collected data on schizophrenia symptoms, as measured by the Positive and Negative Syndrome Scale (PANSS), and analyzed data using an adaptive clinical assay (ADA).

Results: User research data informed the initial version of Pear 004, which was used in a two-week open-label study (n=12; mean PANSS change: -1.0, standard deviation [SD]: 6.62). Data from this study plus additional user research informed a second iteration of the therapeutic, used in an eight-week, open-label study (n=25), to be completed in September 2018. Dosing, engagement, and user research will again be used to inform Pear 004 development ahead of a proof-of-concept, randomized control trial (n=102), starting in Q4 2018.

Conclusion: Using this approach, we were able to refine the content of Pear 004 three times in six months, resulting in a product that is optimized for patient use and efficacy. The opportunities for therapeutic testing and refinement in rapid cycle represent the distinct advantages of agile, data-driven development over traditional drug development.

Funding/Disclosures: None of the authors have any disclosures.

Comparison of structured and free text-based features for re-hospitalization prediction

Presenters: Shao Y,[1] Cheng Y,[1] Zeng-Treitler Q,[1] and Gottipati S[2]

Affiliations: [1]Biomedical Informatics Center, School of Medicine and Health Sciences, George Washington University, and VA Medical Center, Washington DC; [2]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, New Jersey

Background: Clinical risk prediction has been referred to as a cornerstone of modern medicine. The benefit of adding free text-based features from clinical notes to structured data features for risk prediction has not been studied extensively.

Objective: The goal was to compare the significance of free text features with or without structured features in the prediction of re-hospitalization risk among patients with severe mental illness.

Design: Our study cohort was 139,830 veterans with serious mental illness (e.g., schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder). Structured features included demographics, diagnoses, medications, procedures, and note types. Unstructured features were topics identified using a topic modeling method from clinical notes. The logistic regression models were built for 30-day and three-year re-hospitalization. For each outcome, we created three logistic regression models using 1) structured features only; 2) free text features only, and 3) both structured and free text features as predictors. We compared the prediction performance across the models.

Results: All models achieved a c-statistic estimate in the range of 60 to 70 percent. Using structured and free text features alone, re-hospitalization risk prediction performances are almost identical. When combined, prediction performance improved by two percent. Pearson correlation tests have also evidenced that individual free text features are not duplicates of structured features.

Conclusion: Adding free text features from clinician notes did not significantly improve prediction compared to using structured features alone, though free text features alone are equally effective. In future work, we plan on including the entire patient journeys and sentiments from notes, which might further help improve the models.

Funding/Disclosures: This study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, New Jersey.

GaitWayXR: Extended reality games for motor skills assessment and intervention in developmental disabilities

Presenters: Hocking DR,[1] Talbot V,[2] Attard J,[2] and Lenroot R[3]

Affiliations: [1]Developmental Neuromotor and Cognition Lab, School of Psychology and Public Health, La Trobe University, Melbourne, Australia; [2]Playing Forward LLC; [3]Department of Psychiatry and Behavioral Sciences, University of New Mexico, Albuquerque, New Mexico

Objective: Although motor neurological deficits are the most striking and pervasive of impairments in children with developmental disabilities, the currently available clinical and observational assessments lack sensitivity to overcome developmental problems, including language and attention problems. Furthermore, interventions for motor dysfunction tend to focus on less quantifiable social communicative symptoms and apply a "one-size-fits-all" approach to rehabilitation.

Our objective is to develop a personalized approach to detect movement kinematics and variability using machine learning algorithms

and low-cost motion capture technology to identify signature motor patterns indicative of functional and diagnostic status. Another aim is to design a game-based therapeutic intervention and evaluate its effectiveness in a randomized, controlled trial in children with autism spectrum disorders (ASD).

Design: First phase is a case control validation study of 100 school aged children with ASD and 100 age-matched healthy controls to compare movement patterns in a real-time virtual environment to conventional clinical and cognitive assessments. Second phase will involve a double blind, parallel group, randomized controlled trial (RCT) with a 2 (GaitWayXR intervention, control with usual treatment) x 3 (occasion: baseline, posttraining, and 3-month follow-up) mixed design. An intent-to-treat approach will be used to assess intervention effects on the primary (McCarron Assessment of Neuromuscular Development) and secondary (ADOS; NIH toolkit; Behaviour Rating of Executive Function; Social Skills Improvement System; Vineland) outcome measures.

Conclusion: The findings from the validation study and RCT will improve the sensitivity of motor assessments and endpoints for clinical trials and evaluate a real-time, dynamically responsive virtual environment for intervention in children with developmental disabilities.

Funding/Disclosures: Darren Hocking, PhD—(unpaid) Advisor, Playing Forward; Rhoshel Lenroot, MD—(unpaid) Advisor, Playing Forward; Victor Talbot—Co-founder, Chief Inspiration Officer, Playing Forward

Implementing an innovative, scalable, risk-based monitoring strategy

Presenters: Torche F
Affiliations: Director of CluePoints
Objective: Each organization faces different challenges when it comes to implementing risk-based monitoring (RBM) and data quality oversight. There is no "one-size-fits-all" approach that overcomes all the barriers because each organization has specific influencing factors, such as therapeutic area, existing processes and the available technologies. The objective is to explore how organizations are scaling their RBM and medical review approach relying on automated statistical methods.

Design: Presenters explore how automated statistical methods can highlight atypical sites, patients, and clinical parameters to support the centralized monitoring activities, and how those methods can be used as an innovative solution to guide the medical review.

Results: Practical examples are presented that demonstrate how the methodology can be applied in actual trials.

Conclusion: The implementation of an RBM approach requires current processes to be adapted and redesigned for sponsors and CROs to realize its full benefits. Automated statistical methods and visualization tools can support an RBM strategy and medical review by analyzing clinical data to identify risks arising from a lack of training, misunderstanding, carelessness, negligence, or even fraud.

Funding/Disclosures: Funding/disclosure information was not provided.

Increasing clinical trial engagement through AI and voice assistants

Presenters: Beckstrom K
Affiliations: ERT Innovation Lab
Objective: The goal was to test the usability of voice assistant technology to collect patient-reported outcomes (PROs) during a clinical trial and to evaluate if a voice assistant would enhance the participation experience.

Design: An interactive voice questionnaire was created, which allowed subjects to hear the questions and verbally respond to five quality of life questions using a commercially available voice assistant. Over a period of one week, 15 healthy subjects listened to the patient-reported outcome questionnaire and responded verbally. Afterward, they provided feedback on their experience via a survey and interview.

Results: When asked about the experience, people called out several advantages to the use of voice assistance technology, as well as potential concerns to be addressed prior to use in a full clinical trial.

The identified advantages included ease of use, as well as being hands-free, inclusive, and enjoyable. Identified concerns with the technology included problems understanding strong accents and privacy issues.

Conclusion: Participants reported that the voice questionnaire was easy to use and an enjoyable experience. Despite some specific concerns, AI assistants used in this project, such as Amazon's Alexa, have the potential to be used in the collection of patient-reported outcomes and could be a useful mechanism by which individuals with certain limitations could provide their outcome data.

Funding/Disclosures: ERT performed the proof of concept and usability study.

Individual differences in patient behavior as a basis for personalized treatment

Presenters: Smayda KE, Shapiro HM, and Maricich YA
Affiliations: Pear Therapeutics, Boston, Massachusetts
Objective: Prescription digital therapeutics (PDTs) capture idiosyncratic patient behavior that can be leveraged to personalize treatment across clinical populations. We present examples of treatment-relevant behaviors aggregated from patient engagement data within the framework of Pear 004, a PDT for patients with schizophrenia.

Design: Twenty individuals with a *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition* (DSM-V) diagnosis of schizophrenia received Pear 004 for eight weeks, and user engagement data were collected. For every relevant action taken in Pear 004 by a patient, "events" were sent to a database that characterized the nature of the action taken, creating a timestamp, patient ID, and additional properties unique to each event. Possible types of events and event properties were pre-specified during Pear 004 development. Raw events data were then aggregated to capture group level trends and individual differences in Pear 004 use during treatment.

Results: Data collected suggest there are individual differences in how patients use Pear 004. Individual differences were found in engagement measures, such as time spent using Pear 004 and its functionally distinct therapeutic components, hours of the day when used, and the range of lessons and skill topics completed by patient users.

Funding/Disclosures: Pear 004 captures variation in engagement behavior at the individual level and in the context of the patient treatment journey. Differences in

user engagement and experience inform and allow improvements to be incorporated into Pear 004 through iterative therapeutic development. In addition, patient-specific data offer an avenue to personalized, phenotypically driven, and enhanced treatment.

Funding/Disclosures: None of the authors have any disclosures.

Quantitative structure-activity relationship modeling of prescription digital therapeutics

Presenters: Shapiro HM, Smayda KE, and Maricich YA

Affiliations: Pear Therapeutics, Boston, Massachusetts

Objective: In pharmacology, quantitative structure-activity relationship (QSAR) models are mathematical models that test relationships between the chemical components of a drug and its pharmacological effect. The goal is to determine the compound responsible for a biological outcome, enabling potency modulation and optimization of clinical outcome in the target population.

The data-rich characteristics of prescription digital therapeutics (PDTs) lend enormous potential to apply QSAR modeling to the study of features responsible for the impact and potency of this entirely new class of therapeutics.

Design: Engagement/use of the software represents a measure of exposure within PDT. Data will be collected from at least 500 patients, from whom therapeutic application engagement/use and clinical outcome data are accessible. Statistical models will be optimized to identify the importance of engagement/use features as they relate to clinical outcome.

Results: Feature selection will consist of engagement/use variables, including time spent in app, consistency of app engagement, app proficiency, and time/consistency of specific activities within the app. Given the combination of categorical and continuous variables, we will use decision tree statistical models. Models will be validated and accuracy assessed.

Conclusion: Given the unprecedented granularity of patient engagement/use and adherence data with PDT, QSAR modeling might be a powerful method for identifying and optimizing the impact and potency of engagement components on clinical outcome, thus informing therapeutic development in a strategic manner. These models could also potentially be used to predict clinical outcome sooner, leading to earlier and optimized intervention.

Funding/Disclosures: Drs. Shapiro, Smayda, and Maricich are employees of Pear Therapeutics, Inc.

EARLY IDENTIFICATION, PREDICTIVE TOOLS, AND IMAGING

Computerized gait analysis of dual tasks to improve eligibility and outcomes for Alzheimer's disease clinical trials

Presenters: Rosenfeld A, Tolea MI, and Galvin JE

Affiliations: Comprehensive Center for Brain Health, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida

Objective: Clinical trials in Alzheimer's disease are expanding to test compounds in the prodromal states of the disease; however, it is difficult to detect these prodromal states. We investigated whether computerized gait analyses focusing on changes in gait velocity (>15%) associated with single and dual tasking could identify individuals with underlying preclinical disease and be used as a clinical outcome to assess treatment response.

Design: A cross-sectional study of 246 older adults (age: 77.2±7.9 years; 5.6% controls, 27.3% mild cognitive impairment, 67.2% dementia) underwent comprehensive clinical-cognitive characterization. Computerized gait analyses using the 4'x20' Zeno Walkway and ProtoKinetics Movement Analysis Software (PKMAS) tested associations between gait velocity decrease from single task (walking only) to increasing cognitive load dual tasks (walking while talking, walking while subtracting) and extent of cognitive impairment, particularly frontal-executive function.

Results: Velocity declined with increasing cognitive load: 102.6cm/s on single tasks, 100.6cm/s while talking (7.8% decline, p=0.001), and 84.9cm/s during serial subtraction (22.1% decline, p=0.005). Correcting for multiple comparisons (p<0.002), changes in gait velocity correlated with cognitive performance particularly executive tasks (Montreal Cognitive Assessment [MoCA] Clock drawing, total MoCA, Trailmaking A and B, Number-Symbol Substitution), episodic memory (MoCA recall, Hopkins Verbal Learning Test), and verbal fluency (animal naming). A greater than 15-percent decline in gait velocity with dual tasking was strongly correlated with the Clinical Dementia Rating-Sum Boxes.

Conclusion: Computerized gait testing using single and dual task paradigms might potentially detect individual at risk for cognitive impairment as well Mild Cognitive Impairment Questionnaire (MCI) individuals who are likely to progress to dementia.

Funding/Disclosures: Study supported by grants from the National Institutes of Health. The authors have no conflicts to report.

Early prediction of high-risk patients is an opportunity for early intervention

Presenters: Shapiro HM, Smayda KE, Luderer HF, and Maricich YA

Affiliations: Pear Therapeutics, Boston, Massachusetts

Objective: Patient dropout in substance treatment programs is a major challenge, limiting the effectiveness of treatment for patients with substance use disorder (SUD). Prescription digital therapeutics (PDT) could afford a unique opportunity for early intervention by predicting patients at risk of dropout. We tested the predictive nature of early engagement with a PDT on downstream PDT engagement and treatment dropout.

Design: Data were collected from 249 patients with SUD undergoing 12-week treatment with the reSET® PDT (academic name Therapeutic Education System). The PDT was used by 119 (47%) patients for the duration of treatment (defined by PDT engagement during week 12). To identify early signals of dropout, we extracted engagement features from Week 1 of treatment and built a statistical model to predict if a patient remained in treatment for the study duration (a random forest model using an 80–20% train-test ratio).

Results: Five early engagement features measured within Week 1 were predictive of therapeutic retention: number of days that a patient engaged with the PDT, average

proficiency on PDT assessments, consistency of PDT usage, total number of lessons completed, and total anxiety score on the pre-treatment questionnaire. We predicted patient dropout outcomes with 70-percent accuracy.

Conclusion: By leveraging the data-rich characteristics of a PDT, we potentially could identify high-risk patients as early as one week into treatment. This type of prediction can be a powerful method for identifying patients with SUD who might benefit from early outreach and greater support. With early intervention, more patients might complete the 12-week duration reSET treatment, achieving better outcomes.

Funding/Disclosures: Funding/disclosure information was not provided.

The Festination Index: a novel computerized gait analysis task to predict neurodegenerative disease

Presenters: Tolea MI, Rosenfeld A, and Galvin JE

Affiliations: Comprehensive Center for Brain Health, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida.

Objective: Alzheimer's disease (AD) likely begins years prior to the detection of clinical symptoms, yet preclinical and prodromal states are difficult to detect without expensive and invasive biomarkers. We hypothesize readily detectable clinical biomarker analysis could identify individuals with underlying pathology at risk for AD and provide easy-to-measure clinical outcomes.

Design: A cross-sectional study of 246 older adults (age: 77.2±7.9y; 5.6% controls, 27.3% mild cognitive impairment, 67.2% dementia) underwent detailed clinical-cognitive characterization. Computerized gait analyses with the 4'x20' Zeno Walkway and ProtoKinetics Movement Analysis Software (PKMAS) was used to develop a new metric of number of steps per standardized distance—the Festination Index (FI). FI captures the normal walking pattern of a patient over a 40-foot distance and can provide reproducible objective markers of frontal lobe function while also capturing other metrics of the gait cycle. We then tested whether increasing FI is a marker of poorer cognitive performance that could be used as a outcome in clinical research.

Results: The FI increased significantly across cognitive stages from controls (1.5±0.2),

Mild Cognitive Impairment Questionnaire (MCI) (1.7±0.4), and dementia (1.9±0.5). Using a cut-point of 1.65, individuals with FI greater than 1.65 had worse performance on Montreal Cognitive Assessment (MoCA) ($p<0.001$), Number span backwards ($p<0.006$), Trailmaking A ($p<0.008$), Animal Naming ($p<0.001$), and Clinical Dementia Rating-Sum Boxes ($P<0.001$).

Conclusion: Computerized gait analyses not only provide reproducible measures of the gait cycle but also novel metrics of frontal lobe function, such as FI, that can be used to detect individuals at risk for dementia and as an outcome measure in clinical trials.

Funding/Disclosures: The study was supported by grants from the National Institutes of Health. The authors have no conflicts to report.

Phenotype fingerprinting of bipolar disorder prodrome

Presenters: Shao Y,[1] Cheng Y,[1] Zeng-Treitler Q,[1] and Gottipati S[2]

Affiliations: [1]Biomedical Informatics Center, School of Medicine and Health Sciences, George Washington University, and VA Medical Center, Washington DC; [2]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, New Jersey

Background/Objective: Bipolar disorder (BD) is a serious mental disease with heavy socioeconomic and personal burdens. Accurate characterization of BD prodrome can facilitate early identification and intervention programs. The objective was to create prodromal phenotype fingerprints for patients with BD.

Design: Twenty thousand patients with at least two BD diagnoses were randomly selected from the VA Clinical Data Warehouse. We represented each patient's medical history (i.e., hospitalizations, diagnoses, medications, vitals, lab results, and BD symptoms) within the 12 months of BD onset in a temporal image. K-means clustering analyses of the temporal images were performed. "Temporal blurring" was first applied to the images, and then the Euclidean distances on the "blurred" images were calculated for clustering purpose. The images in each cluster were then aggregated, and the mean of each pixel was calculated to form the phenotype

fingerprint of the cluster. K was determined using the elbow method. We then compared the one-year outcomes (psychosis, mortality, hospitalization, and length of hospital stay) of the clusters.

Results: Our analyses yielded eight clusters based on prodromal data and produced eight prodromal fingerprints. The clusters are statistically significantly different on all outcomes (all p-values <0.01) and have different clinical characteristics. Furthermore, we found the length and frequency of prodromal symptoms, such as depression and anxiety, appeared to be associated with clinical outcomes.

Conclusion: Phenotype fingerprint based on the temporal prodromal symptoms are associated with different BD outcomes and can potentially assist providers in identifying patients at risk of adverse outcomes.

Funding/Disclosures: This study was funded by Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, New Jersey.

Reduced polysomnography and wrist actigraphy—reasonable alternatives to standard polysomnography?

Presenters: Dorffner G,[1,3] Kemethofer M,[1] Saletu-Zyhlarz G,[2] Simeoni M,[3] Rainer L,[3] Parapatics S,[1] Loretz E,[1] and Gruber G[1]

Affiliations: [1]The Siesta Group; [2]Medical University of Vienna, Department of Psychiatry and Psychotherapy; [3]Medical University of Vienna, Section for Artificial Intelligence and Decision Support, Vienna, Austria

Objective: The goal was to compare both a reduced electrophysiological montage and actigraphy with full polysomnography (PSG) as viable alternatives to measure sleep in CNS clinical trials.

Design: Twenty healthy subjects (aged 20–29 years) participated in the study. A reduced montage including two EOG electrodes placed 1cm above the outer cantus of the left eye (LOC) and below the outer cantus of the right eye (ROC) referenced versus A2, and wrist movement via an activity monitor was used in parallel to a standard PSG using the EEG channels F4-A1, C4-A1, and O2-A1, submental EMG, and two EOG electrodes placed 1cm above ROC and below LOC, both referenced versus A1.

All PSG recordings were analyzed using a validated computer-assisted scoring system. Actigraphy data was analyzed into Sleep-Wake scores using validated computerized algorithms. Target variables included total sleep time (TST) and sleep efficiency (EFF). For comparison between methods the 90-percent (1-2α) confidence interval (CI) for our target variables was calculated and compared with a defined equivalence interval (EI: taken as the difference between two experts when manually scoring a PSG).

Results: Comparing full and reduced PSG, equivalence was proven for both variables TST (CI= -9.6 +5.9; EI= -18.5 +18.5), and EFF (CI= -1.0 +1.7; EI= -4.1 +4.1), while this could not be shown when comparing full PSG with actigraphy derived TST (CI= -21.3 +7.3; EI= -18.5 +18.5), and EFF (CI= -4.6 +1.5; EI= -4.1 +4.1).

Conclusion: Both alternative methods showed only minor deviation from the gold-standard (full PSG) concerning TST and EFF, but only for the EEG-based reduced PSG solution equivalence could be proven.

Funding/Disclosures: This work was partly funded by the Vienna Center for Innovation and Technology (ZIT). Georg Dorffner, Manuel Kemethofer, Silvia Parapatics, Erna Loretz and Georg Gruber are employees and shareholders of The Siesta Group, a service provider for measuring electrophysiological signals including sleep in clinical trials.

INVESTIGATIVE DRUG THERAPIES/ COMPOUNDS

Differential treatment effects of TNX-102 SL*, a sublingual formulation of cyclobenzaprine, on dissociative symptoms of derealization and depersonalization in a military-related PTSD population: retrospective analysis of a double-blind randomized study

Presenters: Sullivan GM
Affiliations: Tonix Pharmaceuticals, Inc
Objective: Dissociative symptoms are associated with trauma disorders including posttraumatic stress disorder (PTSD). This is retrospective analysis of the treatment effects of a sublingual formulation of cyclobenzaprine (TNX-102 SL) on depersonalization and derealization in a Phase II study of TNX-102 SL for military-related PTSD (AtEase).

Design: AtEase, a double-blind, placebo-controlled, multicenter study of TNX-102 SL in military-related PTSD, randomized 245 participants. The modified intent-to-treat population included 92 on placebo, 90 on TNX-102 SL 2.8mg, and 49 on TNX-102 SL 5.6mg. Depersonalization and derealization symptoms were assessed as part of the Clinician-Administered PTSD Scale for *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition* (CAPS-5) at baseline, Weeks 2, 4, 8, and 12, with the primary endpoint at Week 12.

Results: For the derealization item, 49 of 231 (21.2%) scored greater than zero at baseline; for the depersonalization item, 47 of 231 (20.4%) scored greater than zero. There were 72 participants who met the dissociative subtype (31.2%): 25 had derealization symptoms alone, 23 had depersonalization symptoms alone, and 24 had both. Baseline depersonalization and derealization both correlated with CAPS-5 total, hyperarousal cluster, and sleep disturbance item scores (all $p<0.05$). TNX-102 SL 2.8mg (n=19; $p<0.05$) and 5.6mg (n=12; $p=0.001$) had a significant effect for reducing derealization compared with placebo (n=18). Neither dose reduced depersonalization over placebo.

Conclusion: In the subset with derealization at baseline, TNX-102 SL significantly and dose-dependently reduced derealization over 12 weeks of treatment but had no effect on depersonalization. This differential treatment effect, demonstrated by pharmacological dissection with TNX-102 SL, suggests derealization and depersonalization are separate and distinct neurobiological constructs.

Funding/Disclosures: The AtEase study was funded in whole by Tonix Pharmaceuticals Inc. Dr. Sullivan is an employee of Tonix Pharmaceuticals Inc and owns stock in the company. *TNX-102 SL is an investigational new drug and has not been approved for any indication.

Impact of innovation in neurology drug development

Presenters: Olugemo K,[1] Gertsik L,[2] Kanis K,[1] Park L,[1] Akers N,[1] and Grignolo A[1]
Affiliation: [1]PAREXEL International; [2]California Clinical Trials Medical Group
Objective: The goal was to present evidence on select innovations in neurology clinical

trials and their impact on trial efficiency, likelihood of drug launch, and global patient access.

Design: Central nervous system (CNS) drugs take longer on average to develop than drugs in other therapeutic areas and are half as likely to reach the market. The Economist Intelligence Unit and a panel of drug development experts identified the most promising innovations in neurology trials to quantify their impact on trial efficiency, drug launch, and formulary addition in the United States, European Union, and China. Innovations included adaptive trial designs, patient-centric trials, precision medicine trials, and real-world data. Retrospective analysis included 249 drugs from 372 Phase II and III trials between 2012 and 2017 compared to a control group of 3,999 trials from the same period that did not use the selected innovations.

Results: Innovative neurology trials increased likelihood of launch by 23 percent. Recruitment times were reduced by 50 percent in patient-centric trials. A positive trend was observed for earlier listing of drugs using innovative methods in key formularies and national access lists.

Conclusion: The findings quantify the impact of the most promising innovations on trial efficiency and success in launch and obtaining formulary approval worldwide. Barriers to adoption of innovation and future enablers should be further explored.

Funding/Disclosures: Economist Intelligence Unit Report commissioned by PAREXEL. All authors, except Dr. Gertsik, are employees of PAREXEL International. Dr. Gertsik is an employee of California Clinical Trials Medical Group.

Innovative CNS compounds in development for treatment resistant depression, Alzheimer's disease agitation, nicotine dependence, and migraine.

Presenters: Jones A, Kennon K, O'Gorman C, and Tabuteau H
Affiliations: Axsome Therapeutics, Inc. New York, New York
Objective: AXS-05 is a novel, oral, investigational medicine consisting of bupropion and dextromethorphan in clinical development for treatment-resistant

depression (TRD), Alzheimer's disease (AD) agitation, and as an aid to smoking cessation. The mechanism of action of AXS-05 includes N-methyl-D-aspartate (NMDA) antagonism, sigma-1 agonism, and reuptake inhibition of norepinephrine (NE), 5-hydroxytryptamine (5-HT), and dopamine (DA). AXS-07 is a novel, oral, investigational medicine consisting of MoSEIC™ meloxicam and rizatriptan. The MoSEIC technology results in rapid absorption of meloxicam while maintaining a long plasma half-life.

Design: Phase I studies demonstrated the ability of AXS-05 and AXS-07 to provide therapeutic plasma concentrations. AXS-05 is being evaluated in three clinical programs: a Phase III, randomized, double-blind, active-controlled, 12-week study for TRD; a Phase II/III, randomized, double-blind, placebo-controlled five-week study for the treatment of agitation in patients with AD; and a Phase II, randomized, double-blind, active-control, four-week study as an aid to smoking cessation.

Results: Phase I trials with AXS-05 resulted in therapeutic concentrations of dextromethorphan and bupropion. STRIDE-1 (TRD study) is expected to enroll 350 subjects. ADVANCE (AD agitation study) is expected to enroll 435 subjects. The smoking cessation study is expected to enroll 60 subjects.

In a Phase I trial evaluating MoSEIC meloxicam, therapeutic concentrations of meloxicam were attained within 15 minutes. MoSEIC meloxicam resulted in a T_{max}, which was nine times faster than standard meloxicam (0.5 hours vs. 4.5 hours, $p<0.0001$).

Conclusion: AXS-05 is a fixed-dose combination of dextromethorphan and bupropion. Ongoing trials are evaluating AXS-05 in TRD, agitation associated with AD and nicotine dependence. AXS-07 is a fixed-dose combination of MoSEIC meloxicam and rizatriptan in development for the acute treatment of migraine.

Time since trauma in PTSD: Phase 3 multi-center, double-blind, placebo-controlled trial of TNX-102 SL*, a sublingual formulation of cyclobenzaprine, in military-related PTSD (Study TNX-CY-P301)

Presenters: Sullivan GM
Affiliations: Tonix Pharmaceuticals, Inc.

Objective: TNX-102 SL 5.6mg (TNX5.6) was compared to placebo in military-related posttraumatic stress disorder (PTSD) after 12 weeks of treatment.

Methods: This was a double-blind, randomized Phase III study at 44 sites in the United States of patients with PTSD whose trauma occurred during military service since 2001, with baseline severity at least 33 on Clinician-Administered PTSD Scale for *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition* (CAPS-5). Primary endpoint was Week 12 CAPS-5 mean change from baseline (MCFB).

Results: Study was stopped at interim analysis (N=274 randomized) because the primary endpoint did not meet a prespecified continuation threshold. Although TNX5.6 did not separate from placebo at Week 12, it showed activity at Week 4 (least squares mean difference from placebo [LSMDP] of -3.6, $p=0.019$). In a retrospective analysis, time since trauma (TST) was assessed by median (9 years) split of modified intent-to-treat (mITT) population. TST ≤9 years subgroup showed Week 12 improvement in PTSD (LSMDP -5.9, $p=0.039$). Both combat and non-combat trauma types and female participants (11% of mITT) showed numerical improvement in PTSD at Week 12. The most frequent adverse events with TNX5.6 were local administration site reactions. Systemic adverse events were similar to marketed oral cyclobenzaprine drug products.

Conclusion: TNX5.6 showed activity in TST ≤9 years subgroup in military-related PTSD. The TST >9 years subgroup seems to be more difficult to treat or study using present trial design. Together, these findings support a new Phase III trial in mixed civilian and military-related PTSD with TST of nine years or less to confirm TNX5.6 effect on a population with higher proportions of females and non-combat traumas.

MOBILE TECHNOLOGY

A model for researchers to engage in suicide prevention

Presenters: Hendry P,[1] Armstrong K,[2] Barag J,[2] Fowler C,[3] Gutierrez N,[4] Harkavy-Friedman J,[5] Perez E,[3] Saillard J,[6] Vanover K,[6] and Kramer L[7]

Affiliations: [1]Mental Health America, Alexandria, Virginia; [2]Premier Research, Durham, North Carolina; [3]Otsuka, Princeton, New Jersey; [4]Woodland Research Northwest, Rogers, Arkansas; [5]American Foundation for Suicide Prevention; [6]Intra-Cellular Therapies, New York, New York; [7]STARR Coalition, Little Rock, Arkansas

Introduction: The STARR Coalition is a nonprofit organization consisting of thought leaders throughout the pharmaceutical industry, contract research organizations, clinical research sites, and patient advocacy groups. The organization's mission of is to build unbiased, collaborative initiatives to reduce the stigma associated with central nervous system (CNS) disorders and promote research as an option for those seeking help.

A strong link exists between mental illness and suicide. Up to 20 percent of individuals with a diagnosis of mental illness die by suicide. Approximately 90 percent of those who complete suicide experience mental illness. People considering suicide usually seek help—approximately 64 percent of individuals who attempt suicide visit a doctor within a month before their attempt.[3] Having a chronic condition increases the odds of suicide by 363 percent.

Clinical research call centers field thousands of calls on a yearly basis. The purpose of project STARR 911 is to build collaboration between clinical research and suicide prevention. The first step is to identify current practices.

Methods: We surveyed clinical research sites to identify current practices for recognizing suicidal ideation among callers and taking action.

Results: Preliminary results indicated that some clinical research sites have scripts for their call centers and suicide hotline information readily available. It was generally agreed that national experts in suicide prevention are preferred referral sources over local resources that can vary in accessibility and quality. Script suggestions included asking about intent to act and how long the caller has felt suicidal, to determine the acuity. Creating a designated "warm" line

for call centers and sites to use to transfer individuals with potential suicidal ideations was discussed; a specific hotline for clinical research referrals would make tracking easier. Evaluation is ongoing, and an update on activities will be provided.

Discussion: In response to the limited process identified, Project 911 will identify intervention resources that could be provided to callers. A short script and best practices for recognition and de-escalation and a brief training program that could be made widely available and implemented will be developed. For example, a suicide prevention program can be disseminated at investigator meetings. A tracking system to record number of successful referrals or "warm" hand-offs to suicide prevention specialists will be implemented, if possible.

Conclusion: Research can be a part of the solution to suicide prevention. Potential suicidal ideation or behavior can be identified through clinical research call centers and referred to national suicide prevention experts in a systematic way for broad-reaching impact.

Funding/Disclosures: Funding/disclosure information was not provided.

Predictive value and test-retest reliability of the tablet-based Brief Assessment of Cognition (BAC app) for assessment of cognition in aging: preliminary findings from an ongoing normative study

Presenters: Keefe RSE

Affiliations: NeuroCog Trials, Durham, North Carolina; Duke University, Durham, North Carolina

Objective: The Brief Assessment of Cognition (BAC) app is a brief tablet-based assessment of multiple cognitive domains. We examined the criterion validity of the BAC app for the assessment of cognition in individuals with subjective cognitive decline by assessing the diagnostic sensitivity, specificity, and test-retest reliability of the BAC app endpoints.

Design: In total, 584 participants were enrolled (245 healthy young adults [YA], <55 years; 277 healthy older adults [OA], ≥55 years; 62 individuals with cognitive complaints). Participants with cognitive complaints were categorized based on total scores of at least 4 on the Mail-In Function Cognitive Screening Instrument (MCSFI). Receiver operating characteristic (ROC) analysis and intraclass correlation (ICC) coefficient were computed.

Results: For the YA group, ICCs ranged from 0.558 (Tower of London) to 0.817 (Verbal Fluency) and 0.836 for the cognitive composite; for the OA group, ICCs ranged from 0.487 (Tower of London) to 0.818 (Verbal Fluency) and 0.881 for the cognitive composite; for individuals with cognitive complaints, the ICCs were higher than YA and OA groups and ranged from 0.747 (Token Motor) to 0.836 (Verbal Fluency) and 0.888 for the cognitive composite. The area under the curve (AUC) of the BAC app when comparing YA to individuals with cognitive complaints was good: 0.80 (95% CI: 0.70, 0.83). When a cut-off point of 1.5 SD was used, individuals without cognitive complaints were accurately identified 96.75 percent of the time (specificity).

Conclusion: The BAC app has good discriminative validity in terms of specificity and predictive value for categorizing cognitive decline. It also has good test-retest reliability, with higher test-retest observed for individuals classified with subjective cognitive decline.

Fundings/Disclosures: Dr. Keefe currently or in the past three years has received investigator-initiated research funding support from the Department of Veteran's Affair, Feinstein Institute for Medical Research, GlaxoSmithKline, National Institute of Mental Health, Novartis, Psychogenics, Research Foundation for Mental Hygiene, Inc., and the Singapore National Medical Research Council. He, currently or in the past three years, has received honoraria or served as a consultant or advisory board member for AbbVie, Akebia, Amgen, Asubio, AviNeuro/ChemRar, BiolineRx, Biogen Idec, Biomarin, Boehringer-Ingelheim, Eli Lilly, EnVivo/FORUM, GW Pharmaceuticals, Janssen, Lundbeck, Merck, Minerva Neurosciences, Inc., Mitsubishi, Novartis, NY State Office of Mental Health, Otsuka, Pfizer, Reviva, Roche, Sanofi/Aventis, Shire, Sunovion, Takeda, Targacept, and the University of Texas South West Medical Center. Dr. Keefe receives royalties from the BACS testing battery, the MATRICS Battery (BACS Symbol Coding) and the Virtual Reality Functional Capacity Assessment Tool (VRFCAT). He is also a shareholder in NeuroCog Trials and Sengenix.

PATIENT ASSESSMENT

Do the symptoms that drive the CGI vary by geography?

Presenter: Daniel DG and Kott A

Affiliation: CRF Bracket

Background/Objective: We have previously demonstrated regional differences in measurement of psychiatric symptoms. Global clinical trials in schizophrenia pool data using the Clinical Global Impression (CGI) to assess overall severity of illness. We hypothesized that the symptom constellations driving the CGI would be impacted by cultural norms associated with geography. The current analysis will address regional differences in the relationship among symptoms measured by the Positive and Negative Syndrome Scale (PANSS) and the CGI in clinical trials in patients with acute schizophrenia.

Methods: In the planned post-hoc analysis, baseline and last visit data from 3,831 subjects participating in eight Phase II and Phase III acute schizophrenia studies will be analyzed.

We will assess whether the relationship among the CGI and schizophrenic symptoms measured by the PANSS varies among geographic regions (Asia, Eastern Europe, Western Europe, North America, South America). The relationship between the CGI and 1) PANSS total score, 2) PANSS positive subscale, 3) PANSS negative subscale Negative Factor score, 4) PANSS expressive deficits subscale (N1, N3, N6, G5, G7 and G13) and 5) PANSS avolition/apathy subscale (N2, N4 and G16) will be examined at baseline and at endpoint. Correlation coefficients between CGI and respective measures will be bootstrapped from the data. Analogous analyses will be conducted to assess regional effects on relationship between change in the CGI and change from baseline to endpoint in PANSS measures. All raters received standardized training for assessment of the PANSS and CGI.

Funding/Disclosures: Financial support was provided by Bracket Global, LLC.

An electronic Overt Aggression Scale, Modified (OAS-M) for the measurement of intermittent explosive disorder

symptoms: Correspondence of paper and electronic versions

Presenters: Busner J,[1] Coccaro EF,[2] Silverman S,[1] Dries J,[1] Oakley M,[1] Kott A,[1] and Wang X[1]

Affiliations: [1]Bracket, Wayne, Pennsylvania; [2]University of Chicago, Chicago, Illinois

Objective: The Overt Aggression Scale, Modified (OAS-M) is an often-used primary efficacy measure in industry and government-funded trials of problematic aggression and intermittent explosive disorder (IED). The scale classifies aggressive episodes into four types, with within-episode behaviors weighted in severity, yielding an overall total aggression score. The scale requires considerable training and practice, as well as a semi-structured interview, as defined in an 89-page manual. To facilitate consistent and accurate administration and decrease computation errors, we created an electronic (eCOA) OAS-M that provided per-item instructions, scoring conventions, and automated calculations of episodes, weighted episode severity, and total aggression scores. In this study, we examined the score correspondence of the electronic and paper versions using a series of standardized patients. We hypothesized that the paper and electronic scoring systems would yield similar scores among trained raters across a series of patients with IED.

Design: Four raters trained by the scale author independently rated eight videotaped patients with IED using both the paper and the electronic OAS-M scales, counterbalanced for order, with at least 48 hours intervening between scale types. Agreement of paper and electronic scores was calculated using Intraclass Correlation Coefficients (ICCs).

Results: Per rater and combined rater/patient ICCs ranged from 0.97 to 1.00, demonstrating excellent agreement of paper versus electronic scoring.

Conclusion: The results support the equivalence of the paper and eCOA OAS-M. eCOA-embedded instructions and automated scoring are expected to improve administration and scoring accuracy, both reducing variability and expanding the potential utility of the scale to a wider range of clinical trials raters.

Funding/Disclosures: Data were previously presented at the American Society of Clinical Psychopharmacology Annual Meeting, May 29 to June 1, 2018, Miami, Florida. Dr. Coccaro is on the Scientific Advisory Board of Azevan Pharmaceuticals and is consultant to Avanir Pharmaceuticals, Inc. All other authors are full-time employees of Bracket.

How does NSA-16 Global Score change from baseline relate to other measures of change—an exploratory post-hoc analysis

Presenters: Kott A and Daniel DG
Affiliations: CRF Bracket

Background/Objective: We have previously reported on the convergent and divergent validity of the Negative Symptom Assessment (NSA16) global item with respect to NSA total score, Positive and Negative Syndrome Scale (PANSS) negative factor score, PANSS negative subscale score, Personal and Social Performance Scale (PSP) score, Clinical Global Impression—Severity scale (CGI-S) negative, CGI-S, PANSS Positive factors score, and PANSS positive subscale score. In the current analysis, we wanted to establish the relationship between the change from baseline in NSA16 global item and change from baseline in the above mentioned measures.

Design: We used subject visit data from multiple schizophrenia clinical trials in negative symptoms. The relationship between the change from baseline in NSA Global score and the change from baseline in NSA-16 total score, CGI-S score, CGI-S negative score, PANSS, PANSS Negative factor score, PANSS negative subscale, PSP, PANSS Positive factors score, and PANSS positive subscale score was assessed using polyserial and polychoric correlations as appropriate.

Results: The dataset consisted of 19,738 subject visits collected from 2,567 subjects. The change from baseline in NSA global score demonstrated strong and significant relationship with the change from baseline in NSA total (0.74 ± 0.0038), CGI-S score (0.66 ± 0.0048), CGI-S negative score (0.80 ± 0.0000), PANSS (0.70 ± 0.0049), PANSS negative factor score (0.60 ± 0.0052), PANSS negative subscale score (0.60 ± 0.0052), and PSP (-0.62 ± 0.0071). As expected, weaker correlations were observed with the change in PANSS Positive factor (0.42 ± 0.0081) and PANSS positive subscale (0.38 ± 0.0087).

Conclusion: The current results along with the previously reported results on convergent and divergent validity of the NSA Global Score further support the use of the NSA Global Score as a valid outcome in tracking subject's negative symptoms both in clinical practice and during clinical trials.

Funding/Disclosures: Financial support provided by Bracket Global, LLC.

PATIENT RECRUITMENT

Impact and return on investment of patient recruitment campaign in a clinical trial of patients with opioid use disorder

Presenters: Ramos J,[1] Carter D,[1] Romanello S,[2] Miller M,[3] and Martin W[1]

Affiliations: [1]Alkermes, Inc.; [2]PriMedia; [3]StudyKIK

Background: ALK6428-A302 was a Phase III clinical trial that evaluated the efficacy, safety, and tolerability of low doses of oral naltrexone used in conjunction with sublingual buprenorphine (BUP) for adults with opioid use disorder (OUD) transitioning from BUP maintenance therapy (BMT) prior to the first injection of VIVITROL® (naltrexone for extended-release injectable suspension). Recruitment of patients with OUD is a challenging and complex endeavor in a clinical trial setting. Similar to other disease areas, a common deterrent in this population is the concern of receiving placebo. However, there were several unique factors that served as barriers to enrollment of this patient population in the present trial. For example, many BUP providers are reluctant to refer patients to enroll in a clinical study, especially when there is a requirement to taper patients to lower BUP doses. Additionally, given that many patients are maintained on BUP doses greater than 8mg, a unique challenge of this trial was identifying a protocol-specific target population of BUP-maintained patients on an entry dose of only 8mg. Given these challenges, the present trial required innovative patient recruitment strategies that were implemented over the course of the trial.

Objective: The goal was to present the results of a patient recruitment campaign (PRC) and the methodologies utilized to recruit patients in a challenging trial.

Design: This was a Phase III, randomized, double-blind, placebo-controlled, parallel group study. The study was nine weeks in duration and included a 9-to-12 day inpatient

BUP taper/detox with naloxone challenge and VIVITROL administration on Day 8/8a. Patients (N=92) were randomized in a 1:1 ratio to 1 of 2 treatment arms consisting of ascending doses of oral naltrexone and BUP or placebo naltrexone and BUP. Patients were stratified according to low (<8mg/day) versus high (8mg/day) BUP maintenance dose at the time of initiation of the BUP lead-in period (5-day stabilization on 4mg/day BUP). All subjects received a standardized ancillary medication regimen. The patient recruitment strategy used location based out of home (OOH) advertising strategy to target major BUP providers in each metro area, along with traditional advertising techniques (e.g., radio, print). StudyKIK was used, which is a company that connects people to clinical trials through social media communities.

Results: Of the 183 patients screened between January and October 2017, it is estimated that 99 (54%) of the patients were recruited through PRC efforts, and of the 101 patients randomized overall, it is estimated that 46 (46%) patients were recruited through the PRC. As trial enrollment progressed, there was a shift in recruitment sources from site databases to a greater reliance on traditional media and StudyKIK recruitment tatics, which together accounted for approximately half of the recruitment sources by the end of the recruitment period. It is estimated that if the trial were run without any PRC support, while relying solely on site-based efforts, an additional 20 months would have been required to complete enrollment, at an estimated 73-percent increase in operational costs.

Conclusion: The patient recruitment campaign implemented in this trial was effective and resulted in substantial time and cost savings. No apparent differences were observed in key quality metrics of patients recruited from advertising versus non-advertising sources. Using patient recruitment campaigns for this population could be an effective way to reduce clinical trial time and cost as well as provide insight into the most effective types of advertising for this population.

Funding/Disclosures: ALK6428-A302 was an Alkermes-sponsored clinical trial. Jandira Ramos, Denise Carter, and William Martin are currently employed by Alkermes.

Impact and return on investment of patient recruitment campaign in a clinical trial of patients with schizophrenia

Presenters: Carter D,[1] Romanello S,[2] Miller M,[3] and Martin W[1]

Affiliations: [1]Alkermes, Inc.; [2]PriMedia; [3]StudyKIK

Background: ALK3831-A303 is a Phase III study to evaluate the safety and efficacy of a fixed-dose combination of olanzapine and samidorphan (ALKS 3831) compared to olanzapine alone for treatment of adults with schizophrenia (SZ). Historically, the recruitment of subjects with SZ in clinical trial settings is quite variable. For example, inpatient trials of subjects with acute exacerbations of SZ often enroll quite rapidly, whereas outpatient trials of subjects with stable illness tend to enroll much more slowly. In ALK3831-A303, we sought to enroll a challenging population of subjects with stable illness. Key protocol limitations for this population included that patients be 18 to 55 years old, have a body mass index of 18 to 30kg/m^2, and not have recent exposure to olanzapine. These criteria alone were estimated to reduce the number of eligible subjects by more than half. Given these challenges, the present trial required patient recruitment strategies that were implemented over the course of the trial in an effort to increase the rate of enrollment.

Objective: The goal was to present the results of a patient recruitment campaign (PRC) and methodologies used to recruit patients in a challenging trial.

Design: The PRC used a number of strategic site-specific advertising tactics, such as location-based traditional advertising techniques in out of home (OOH), TV, radio, and print. Community outreach efforts were also conducted to further improve awareness about available care. Finally, multiple recruitment vendors were engaged to run social media campaigns to support trial enrollment.

Results: Of the 1,261 patients screened, it is estimated that 583 (47%) patients were recruited through PRC efforts, and of the 561 patients randomized, it is estimated that 221 (40%) were recruited through PRC. As anticipated, clinical trial site databases were depleted as the clinical trial progressed. As a result, there was a shift in recruitment sources to community outreach and TV advertising, which made up more than half of the recruitment sources by study completion. The duration of enrollment was 26 months with an enrollment rate of less than 0.5 subjects randomized per site per month. It is estimated that enrollment would have taken ≈13 months longer if we had not used PRC efforts. Without implementing a robust patient recruitment campaign, the overall trial cost would have been an additional ≈$11 million.

Conclusion: The patient recruitment campaigns used for this patient population could be an effective way to reduce clinical trial enrollment time and cost.

Funding/Disclosures: ALK3831-A303 was an Alkermes-sponsored clinical trial. Denise Carter and William Martin are currently employed by Alkermes.

Unique recruitment strategy utilized by ClinEdge to identify and recruit Rett syndrome patients for a clinical trial

Presenters: Burns C

Affiliations: President, ClinEdge

Objective: ClinEdge conducted a unique patient recruitment strategy to assist our client in meeting enrollment goals for a rare pediatric clinical trial. The challenge was finding patients aged 4 years or older with Rett syndrome, a rare, noninherited genetic postnatal neurological disorder that occurs almost exclusively in girls and leads to severe impairments, affecting nearly every aspect of the child's life, such as ability to speak, walk, eat, and breathe easily. ClinEdge was tasked with developing a unique recruitment strategy, as the incidence is estimated at 1/30,000 in the United States.

Design: ClinEdge team members engaged with potential referral sources, which included neurologists, pediatric neurologists, geneticists, and other Rett syndrome specialists, to increase exposure of this study, inform doctors about the study, and encourage them to discuss the opportunity with the caregivers of patients with Rett syndrome. Once a patient was identified, ClinEdge provided study materials to each referring physician, allowing the caregiver to make an informed decision about this study. If the caregiver was interested in enrolling his or her child, ClinEdge connected the caregiver

with the closest site and provided the contact information to the study staff.

Results: This approach has so far resulted in five referrals that have been sent to the enrolling sites in the United States. One referral is in the screening phase, while the remaining families are communicating with the sites about participation.

Conclusion: By developing a customized marketing strategy for this "tough-to-recruit" study, we were able to help fulfill study enrollment and ultimately progress research for Rett syndrome patients.

Funding/Disclosures: None.

PLACEBO RESPONSE

Classical and quantum machine learning applied to predicting placebo response For clinical trials in bipolar disorder: recent results

Presenters: Geraci J,[1,2] Wong B,[1] Ziauddin J,[1] Jain S,[1,3] Leonczyk P,[1] and Bishop KI[4]

Affiliations: [1]NetraMark Corp, Toronto, Ontario, Canada; [2]Department of Molecular Medicine, Queen's University, Kingston, Ontario, Canada; [3]University of Toronto, Toronto, Ontario, Canada; [4]Global Pharma Consultancy, LLC, Pennsylvania

Objective: The goal of this study was to determine if machine learning can be used to predict placebo response in a consistent way for central nervous system (CNS) clinical trials.

Design: Data obtained from a failed pharmaceutical trial of depression in bipolar disorder was reshaped into a structure suitable for a machine learning platform. The data contained 64 placebo patients and ≈150 variables consisting of clinical data and rating scale data, (e.g., Hamilton Depression [HAM-D] and Montgomery-Åsberg Depression [MADRS]). Despite a small sample size, we postulated our unique technology was capable of learning from data of this size. Validation has been provided by hundreds of tests, but in this case, we sought to validate the model on the drug arm of the failed clinical trial.

Results: A model that can predict placebo non-responders 94 percent of the time has been identified. In brief, there are a set of psychological attitudes that come together in a non-linear way to characterize a type of patient who will not respond to placebo (e.g.,

desire to be part of the trial). No one variable alone can have this efficacy. The model was tested on the drug arm, and 89 percent of those predicted to be non-responders did not respond.

Conclusion: Preliminary results suggest that it's possible to predict placebo response in mood disorder cohorts (bipolar disorder and depression) and placebo non-response with a set of simple attitudinal based measures identified as working together in a non-linear way. Cutting-edge machine learning models that deviate from the typical tree and neural network-based models show promise with small sample sizes and heterogeneous data found in clinical trials.

Funding/Disclosures: Ontario Brain Institute

A first-time investigation of a subject intervention to reduce the placebo and nocebo effects: a multicenter, randomized, single-blind, all-placebo study of a placebo-control reminder script for subjects with major depression

Presenters: Cohen EA,[1] Hassman H,[1] Walling DP,[2] Hoover S,[1] Wyka K,[3] Ball RR,[1] Joseph AV,[1] Lobb JJ,[1] Hazzard-Randolph D,[1] and Ereshefsky L[1,4]

Affiliations: [1]Hassman Research Institute, Science Division; [2]Collaborative Neuroscience Network; [3]The City University of New York, Graduate School of Public Health and Health Policy; [4]Retired Professor, The University of Texas

Introduction: This investigation is the first known to empirically explore whether educating subjects about key causes of the placebo effect can significantly reduce placebo and nocebo effects. The key causes are placebo response factors (PRFs), which include participant expectations of benefit, poor placebo understanding, misconception of expected interactions with site staff, and subject role uncertainty.

Methods: In this Institutional Review Board (IRB)-approved, United States multicenter, single-blind, all-placebo investigation, patients with moderate-to-severe depression, aged 18 to 65, were randomized to the control group (CG; n=40) or intervention group (IG; n=41). IG subjects were read the placebo-control reminder script (PCRS), which reviewed the PRFs before the primary efficacy scale (self-reported Beck Depression

Inventory [BDI-II]) administration. CG subjects were not read the PCRS. Adverse events were also collected to assess side effects. Subjects were informed of the 50-percent chance of being assigned placebo or active drug, yet all subjects received placebo. Given this deception, subjects were provided a debriefing form post-intervention revealing the investigation's true intent and procedures.

Results: Subjects did not differ in baseline characteristics, including BDI-II scores (IG M=33.80, SD=9.08; CG M=31.10, SD=7.28, p=0.144). A significant time-by-group interaction (p=0.018) indicated that IG subjects reported higher BDI-II scores post-intervention (IG M=26.10, SD=1.56; CG M=20.68, SD=7.58). Although not significantly different (p>0.05), fewer IG subjects reported adverse events (IG 31.7%, CG 42.5%), improvement in depression (IG 36.6%, CG 52.5%), and belief they received real medication (IG 36.6%, CG 42.5%).

Conclusion: The PCRS controlled the placebo but not the nocebo effect. Future investigation recommendations will be discussed. If the PCRS is found to be effective in reducing the placebo/nocebo effect, similar scripts read by site staff (e.g., raters) will be recommended.

Funding/Disclosures: All authors have no conflicts of interest or bias in the conclusions of the current investigation or promotion of the current study intervention.

RATER ASSESSMENT AND TRAINING

Interrater reliability of the Protokinetics Movement Analysis Software and the Zeno Walkway during Four Step Square Test in individuals with Parkinson's disease

Presenters: Boddy A, Andrea C, Lomaglio M, Murphy J, and Perry L

Affiliations: University of St. Augustine and S.T.A.R.S Rehab

Objective: There is a growing interest in understanding postural instability in individuals with Parkinson's disease (PD). The purpose of the study was to determine the interrater reliability of the timing of the Four Step Square Test (FSST) in individuals with Parkinson's disease (PD) using the Protokinetics Movement Analysis Software (PKMAS) in a Protokinetics 4'X4' Zeno

electronic walkway compared to a human evaluator using a handheld timer.

Design: A methodological study of 21 participants (age: 74.5±5.4 years) diagnosed with PD (Hoehn & Yahr I–III) while on medication were instructed to perform the FSST sequence on the Protokinetics 4x4 mat while concurrently being timed by an evaluator using a handheld timer. Two trials were performed and then averaged to produce a mean score for the computerized time and manual (evaluator's) time. The mean times were compared to determine reliability.

Results: The PKMAS/Zeno demonstrated excellent reliability ICC=0.99 and Pearson's correlation r=0.99 compared to evaluator using handheld timer.

Conclusion: The FSST is a quick balance assessment that involves stepping over sticks in multiple directions including forward, lateral, and backward, and has been validated to predict fall risk in various neurologic populations. Computerized analysis of the FSST using the PKMAS/Zeno demonstrates excellent reliability to manual timing while providing calculated spatial temporal parameters to further evaluate balance deficits in individuals with Parkinson's disease that could impact fall risk prediction and prevention.

Funding/Disclosures: The authors have no conflict or funding disclosures to report.

Proof of concept (PoC): applying natural language processing (NLP) and machine learning (ML) technologies in clinical trial rater surveillance (CTRS) for near real-time monitoring

Presenters: Lee S
Affiliations: nialas LLC

Objective: For central nervous system (CNS) clinical trials (CT), clinical trial rater surveillance (CTRS) is an important part of data quality monitoring. However, current, CTRS methodology has many limitations due to its reliance on human monitoring, which is 25-to-30 percent coverage of all structured interviews for a given CT. nialas LLC has developed a proof of concept (PoC) technology solution platform (patent pending) that uses NLP and ML to overcome current methodology limitations.

Design: Public data were used that included audio recordings (AR) and their human-

transcribed text files (HTTF). Using the HTTF, 1,422 questions were chosen for surveillance (QfS), after which, each AR was transcribed using an automated cloud service (CS). Transcribed text was analyzed and compared to QfS using NLP and ML. For best sensitivity and specificity, 75-percent match confidence threshold was chosen.

Results: NLP and ML correctly identified QfS with 95.4-percent accuracy. Only 4.6 percent was identified as requiring further human intervention (HMINT).

Conclusion: This PoC suggests that using advanced modern technologies such as NLP and ML could provide 100-percent coverage of CTRS in near real-time for a given CT with minimal HMINT. To further enhance the accuracy, there are two methods to boost the signal: 1) by training ML algorithms with additional dataset, and 2) by employing a connected device that records high-fidelity AR. nialas LLC is exploring an initial pilot study partner who can provide real world CT data.

Funding/Disclosures: This project was funded by nialas LLC. and there are no conflicts related to the content of the poster.

TRIAL PROTOCOL

Evaluation of collecting human emotions and if it could provide valuable evidence in clinical trials

Presenters: Yamamoto R
Affiliation: ERT

Objective: The goal is to present a pilot project evaluating passively collected emotional data during clinical trials to determine its usefulness in supplementing traditional endpoint data.

Design: The 11-person study combined the Columbia Suicide Severity Scale with emotional intelligence software to capture emotional and facial expression during subject use to determine if the data could provide a more comprehensive understanding of the patient.

Results: Participants reported answering the questions honestly and not being distracted by the camera reading their facial muscle movements. Data collected during the experience included engagement, which was indicative of the intensity of subject's facial expressiveness via facial muscle activation,

whether subjects were paying attention during the assessment, and emotion data plotted on a valance scale to indicate the intensity of four key emotions—engagement, fear, joy and sadness.

Conclusion: Acquiring information on engagement, attention, and emotions while a subject completes a self-report assessment appears feasible and does not appear to affect the subject's answers. Analysis of results depends on the nature and goals of the specific assessment with which the software is used. For example, the individual's responses are important in cases where the emotion data appear discordant with reported data. Under different circumstances and with a different assessment, group results could be interesting.

Funding/Disclosures: ERT performed the evaluation and feasibility study.

Impact of the CIRP workflow scheduling tool on the operational efficiency of complex psychiatry trials

Presenters: Saxby BK, McNamara C, Meares K, Yavorsky C, and Di Clemente G
Affiliations: Cronos Clinical Consulting Services, Inc

Objective: Central nervous system (CNS) trials fail for a variety of reasons unrelated to the efficacy of the drug, such as incorrect patient selection, high placebo response, or functional unblinding. The industry has responded with innovative approaches, such as independent eligibility determination, rerandomization of placebo nonresponders, and remote independent ratings. Although these strategies might address the scientific issues, increasing the complexity of trials generates operational challenges that pose a risk to study success. We examined the impact of a role-based and criteria-based workflow scheduling tool designed to improve the operational efficiency of complex trials.

Design: We aggregated metrics from five psychiatry studies in which sites used the cloud-based Cronos Integrated Research Platform (CIRP) to coordinate study-related events across multiple vendors and patients. Activities included online scheduling of blinded, remote raters for conducting clinical assessments, and automated reminders to patients to perform at-home biometric sampling.

Results: Data were collected over 30 months from five studies in 21 countries and 20 languages, involving N=1,962 patients, 142 raters, and 590 registered CIRP users. Event scheduling actions (including attempts/cancellations) totalled 124,513, with 500,000+ active and passive notifications sent to users. Of the 24,201 completed events, 10,115 were cancelled/rescheduled at least once and 2,561 twice or more (i.e., more than 50% of the completed activities encountered operational disruption that could have led to missing data).

Conclusion: The operational impact of increased complexity is not simply a workload issue but can have a direct effect on study data. Tools that can centrally coordinate activities and monitor and produce actionable metrics would be valuable.

Funding/Disclosures: BKS, CM, KM, CY are full-time employees, and GDC is the Founder and President of Cronos Clinical Consulting Services, Inc., developer and commercial provider of the CIRP for use in clinical trials.

Subject training substantially improves understanding of key terminology in gastrointestinal clinical trials

Presenters: Dias N
Affiliations: ERT
Objective: The objective of this study was to examine the effectiveness of training on subject comprehension of terminology often seen in endpoint-related patient-reported assessments in gastrointestinal clinical trials.

Design: In total, 619 participants completed an online survey in which they were asked about their knowledge of rescue laxatives. Demographic data were also collected.

Results: Participants were asked "Imagine you are participating in a clinical trial for constipation and are instructed to take rescue laxative as needed. What is a rescue laxative?" Only 24 percent chose the correct answer, "Any laxative taken to treat constipation other than the investigational medication." Twenty-eight percent selected "Any laxative taken to treat constipation," and 14 percent chose "A laxative used to rescue you from a dangerous situation." The remaining 34 percent selected either "All" or "None of the Above."

A short amount of educational information was then presented: A rescue laxative is a medicine used to stimulate or facilitate a bowel movement when you are experiencing constipation. A rescue laxative is not the investigational medication that is being studied in the clinical trial.

The same question was asked again, in which there was a greater than two-fold increase in participants who chose the correct answer (56%), "Any laxative taken to treat constipation other than the investigational medication." Twenty-six percent selected "Any laxative taken to treat constipation," and three percent chose "A laxative used to rescue you from a dangerous situation." The remaining 15 percent selected either "All" or "None of the Above."

Conclusion: The majority of subjects do not understand the intended meaning of "rescue laxative," a term often used in gastrointestinal studies, which can be detrimental to primary endpoint data. This problem can be remedied in the form of interactive training videos on the trial device, where such definitions and key concepts can be explained and reviewed offline at any time.

Funding/Disclosures: Funding/disclosure information was not provided.

Training clinical trial subjects on accuracy in reporting of patient-reported outcomes improves data quality

Presenters: Dallabrida SM
Affiliations: ERT
Background: Clinical trials routinely rely on patient-reported outcomes (PRO)/electronic PRO (ePRO) data capture to assess drug efficacy and safety. Current endpoints include subjective and objective patient reports. The United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommend use of patient training to improve the quality of clinical endpoint PRO/ePRO data capture in general and therapeutic area-specific-guidances. However, adoption of this recommendation remains slow as biopharmaceutical companies seek further evidence of an effect of subject training.

Objective: A study was conducted (N=514) across indications to test five common, primary endpoints used in clinical trials to capture PRO/ePRO data within subjects pre- and post-training.

Design: Currently used endpoints in gastrointestinal disorders (stool count), central nervous system (CNS) (pain severity), hematology (bleeding event), dermatology (itch severity), and rescue laxatives (event) were tested.

Results: In the five endpoints tested, training significantly improved the number of subjects who selected a correct response (McNemar $p<0.0001$). Pre-training, the mean pain score was 7.9 ± 2.2 and post-training improved to 8.5 ± 1.7 (correct score=9, $t513=5.69$, $p<0.0001$), reducing the standard deviation by 23 percent. Individual effect sizes for training were: stool count (0.85), pain severity (0.85), bleeding event (0.93), itch severity (0.51), and rescue laxative use (1.18). Training significantly improved accuracy for all five PROs. Evaluating the number of correct responses combined across all five PROs pre- and post-training found that training significantly improved overall responses ($t482=17.4$, $p<0.0001$, Cohen's $d=0.77$). Mean (5 PROs) pre-training score was 66.2 percent, and post-training increased to 82.9 percent, demonstrating improved data accuracy across all five PROs with subject training.

Conclusion: Subjects who underwent training improved accuracy of key clinical endpoints across indications, which improved the signal/noise ratio for drug efficacy/safety endpoints and reduced the likelihood of Type I and II errors.

Funding/Disclosures: The study was funded by ERT.

Training on roles and responsibilities and questionnaire meaning is the primary motivation for subjects with arthritis to complete patient-reported outcomes in clinical trials

Presenters: Durand E
Affiliation: ERT
Objective: The goal was to determine what engagement strategies motivate clinical trial patients with arthritis to complete daily patient-reported outcomes (PRO) measures and to investigate how subjects interpret specific items that are routinely presented in a clinical trial setting.

Design: Via an online survey, 147 participants reporting a diagnosis of arthritis (osteoarthritis, psoriatic arthritis, or rheumatoid arthritis) reported on demographics, diagnoses, and socioeconomic

status and identified the motivational strategies that would encourage them to complete PROs in a consistent manner. Participants also reported their level of understanding of common assessment items.

Results: Overall, 66 percent of participants indicated that receiving training on their roles and expectations and/or the importance of the study questionnaires would motivate them most to complete PROs on a daily basis in a clinical trial setting. Eighteen percent reported they would be motivated most by email or text message reminders, followed by monetary compensation (8%), gaining access to games through an app (2%), or other incentives (6%). Fifty-one percent indicated they would be willing to spend up to 60 minutes and 81 percent reported they would spend up to 30 minutes engaging with interactive training materials to review educational information.

Participants were asked to imagine they were participating in a clinical trial for knee arthritis and had to report on the severity of their pain. Without training, 20 percent of subjects indicated they would report on pain in other joints of the body instead of focusing on the arthritic knee. In addition, nearly 25 percent of patients misunderstood items asking them to report knee pain levels in relation to study medication dosing.

Conclusion: Patients with arthritis are motivated by training, above other alternative engagement strategies, to maintain adherence with study questionnaire completion. Questionnaire content that is commonly seen in clinical trials for this patient population can be difficult for subjects to interpret; this variability in interpretation should be addressed with training.

Funding/Disclosures: The authors have no conflict or funding disclosures to report.

Understanding the prevalence of exclusion/inclusion related protocol violations in CNS clinical trials by using Verified Clinical Trials' research subject database registry.

Presenters: Wang Y, Zhang Y, DiBartolo-Cordovano R, Weingard KK, and Efros DE

Affiliations: Verified Clinical Trials

Objective: The goal was to prospectively determine the prevalence of and prevent exclusion/inclusion-related protocol violations (EIPVs) in central nervous system (CNS) clinical trials in the United States from August 2016 to July 2018. EIPVs are preventable protocol deviations that can affect participant safety and data integrity. EIPVs result from subject forgetfulness, deception or inability of researchers to reliably verify subject research history. The prevalence of EIPVs historically has not been well understood due to retrospective or unreliable methods of data collection.

Design: CNS EIPV data were collected from a global research subject database registry utilized at approximately 1,000 sites in the United States (Verified Clinical Trials). Subject partial identifiers were entered into the database after execution of the site-associated instutitional review board (IRB) approved consent form. EIPVs were identified after entries were authenticated and compared to a subject's research history via proprietary algorithm. Participants with EIPVs were prevented from screening.

Results: Among the 374 potential EIPVs identified, 35.0 percent were due to exclusionary research history, 23.8 percent to washout period truncations, 13.4 percent to re-screening/re-enrollment attempts, 12.3 percent to dual enrollment attempts, and 9.4 percent due to dual screening attempts.

Conclusion: Prospective identification of EIPVs is an important way to understand the scope of this problem and to prevent it in CNS trials. Without a research subject database registry, these 374 EIPVs would not have been identified or prevented. We argue that all sponsors would benefit from using a registry such as this registry at their CNS research sites to protect clinical trial participant safety and data integrity.

Funding/Disclosures: All presenters work for the research subject database registry (Verified Clinical Trials) used in this analysis.

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